REMARKS

Claims 14-22 and 33-38 were pending. No claim is allowed.

Rejection Under 35 U.S.C. § 112, first paragraph - enablement

Claims 14-22 and 33 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking reasonable enablement for reasons of records. Specifically, the Examiner asserted that the data submitted in the Reply filed on February 21, 2002 should be presented in a Declaration pursuant to 37 C.F.R. § 1.132. Applicant traverses this rejection.

Applicant respectfully submits that objective data demonstrates that the claimed antibodies effectively treat multiple sclerosis in an animal model regarding as clinically relevant. *See* Exhibit A. Dr. Mihara attests to the experiments performed in the Experimental Allergic Encephalomyelitis (EAE) mouse model, which practitioners in the field regard as a relevant model for multiple sclerosis. *See, e.g.*, Suen et al., *J. Exp. Med.* 186: 1233 (1997) (already of record). Dr. Mihara describes the reduction of symptom severity and duration when mice received the anti-IL-6 receptor antibody. *See* Exhibit A at ¶¶3-4 and Figure 1. Because the EAE model was known as of the effective filing date of the above-captioned application as a relevant model for multiple sclerosis, the antibody effectively mediated treatment of EAE, and sufficient guidance was provided in the specification to use the claimed methods, undue experimentation is not required to use an anti-IL-6 receptor antibody to treat multiple sclerosis.

Accordingly, the basis for this rejection may be withdrawn.

Rejection Under 35 U.S.C. § 103 (a)

Claims 14-22 and 33-38 stand rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Gijbels et al. (1995) in view of Vink et al. (1990) and further in view of U.S. Patent No. 5,605,930 (Samid) for reasons of record. Applicant traverses this rejection.

Applicant respectfully submits that the cited combination fails to render the claimed methods *prima facie* obvious in view of the entirety of the cited documents for reasons of record as well as those discussed below. If the full disclosure of these documents is considered, no teaching or suggestion of the claimed methods can be found, much less a motivation to combine the references or a reasonable expectation of such methods.

The cited combination fails to teach or suggest the claimed methods.

Applicant respectfully submits that the entirety of each reference's disclosure must be considered in the obviousness analysis. *See* MPEP § 2143.02 ("A prior art reference must be considered in its entirety, *i.e.*, as a whole, including the portions that would lead away from the claimed invention.") (emphasis included) (citations omitted). A careful review of the disclosure of Gijbels, Vink, and Samid indicate that each teach away from the claimed methods, and therefore fail to provide either motivation for their combination or a reasonable expectation of success for such a combination.

Gijbels complete teaching regarding IL-6 activity after anti-IL-6 antibody administration fails to predict the exact mechanism of action for the observed clinical effects. The Examiner asserts that Gijbels concludes that antibodies to IL-6 are protective by neutralizing endogenous IL-6 activity. Contrary to these assertions, Gijbels concludes that the effects are likely a combination of neutralization and increased bioactivity. For example, in the abstract Gijbels states:

> Our study indicates that IL-6 plays an important role in autoimmune CNS inflammation. However, due to the complex nature of the *in vivo* interactions of administered antibodies, the disease-reducing effect of the anti-IL-6 antibodies could be caused by neutralization of IL-6 activity or by enhancement of IL-6 activity via induction of higher IL-6 levels in the CNS.

Gijbels at 795 (emphasis added). Moreover, Gijbels discloses evidence that IL-6 bioactivity is actually *increased* following administration of anti-IL-6 antibody. *See, e.g.*, Gijbels at Figure 3. Thus, when read in its entirety, Gijbels lacks any prediction as to how the anti-IL-6 antibody functioned. Gijbels fails to predict whether the antibody neutralized IL-6, interfered with an interaction between IL-6 and its receptor, enhanced circulating levels of IL-6, or some combination of these effects. This ambiguity is acknowledged by the authors in their concluding statement:

> The net result of administration of Ab to a cytokine thus is dependent on the balance between two opposing effects (*i.e.*, neutralization and accumulation). These findings indicate that the mechanisms underlying *in vivo* effect of antibodies to cytokines are complex.

Gijbels at 804 (emphasis added). Thus, contrary to the Examiner's assertion, Gijbels provides no clear indication that blocking an interaction between IL-6 and its receptor confers a protective

or therapeutic effect. Thus, Gijbels lacks any teaching or suggestion that an anti-IL-6 receptor antibody could have been utilized for the treatment of a sensitized T-cell mediated disorder.

Neither Vink nor Samid remedy this deficiency. Vink discloses the use of antibodies targeting IL-6 and its receptor in B cells. T cells or associated diseases are not mentioned in Vink. Likewise, Samid is completely silent regarding the use of an anti-IL-6 receptor antibody to treat T-cell mediated diseases. Samid simply discloses the use of protein decomposition product to inhibit IL-6. Such general teachings fail to teach or suggest that the use of anti-IL-6 receptor antibody in the treatment of T cell-mediated diseases.

Applicant respectfully requests that if the Examiner's rejection is based on facts within his personal knowledge, the Examiner will support this rejection with those facts in an affidavit by the Examiner according to MPEP § 2144.03. According to MPEP § 2144.03,

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner.

Applicant also notes that it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it that supports a given position, to the exclusion of other parts necessary for the full appreciation of what the reference fairly suggests to one of ordinary skill in the art. *In re Wesslau*, 147 U.S.P.Q. 391 (CCPA 1965). The entirety of the disclosure of each reference must be considered.

The cited combination fails to provide a motivation to combine the references.

The motivation to combine set forth by the Examiner relies on incomplete consideration of the cited references and a misunderstanding of the art. For example, Gijbels discloses that anti-IL-6 antibody increases IL-6 bioactivity and *may* neutralize IL-6 binding, speculating that the antibody delays elimination and/or increases IL-6 production. *See* Gijbels at 801, second column. If an antibody to IL-6 receptor were to have similar protective effects as observed in Gijbels, the skilled artisan would seek an antibody that increases IL-6 bioactivity and potentially neutralizes IL-6 binding. There is nothing in Gijbels that teaches or suggests that predicts an anti-IL-6 receptor antibody would have a similar effect. The Examiner has only asserted one aspect of the Gijbels disclosure (*i.e.*, the potential neutralization of IL-6) and disregarded the rest of the disclosure, contrary to the typical practice of one of ordinary skill in the art. Likewise, the rationale provided by the Examiner extrapolates the effects of IL-6 on B cells with that expected in T cells. As noted above, a person of ordinary skill in the art would

not consider experiments performed using a B cell specific growth factor, *i.e.*, IL-6, to have any predictive value for IL-6 activity in T cells, a distinct lymphocyte population. Vink discloses the use of antibodies against IL-6 and IL-6 receptor in malignant B cells. To date, the Examiner has provided no objective evidence demonstrating that one of ordinary skill in the art uses B cell studies to determine strategies for T-cell mediated diseases. Samid relates to the use of a non-antibody reagent to modulate IL-6 expression. Samid is completely silent regarding the use of antibodies. The unpredictability in Gijbels, the lack of relevance in Vink, and the generality of Samid fail to provide motivation to combine the cited references as neither the nature of the problem, the teachings of the prior art, or the knowledge of persons of ordinary skill in the art provide any source for such a combination.

The cited combination fails to provide any reasonable expectation of success.

Given the unpredictability of treating sensitized T-cell disorders with an anti-IL-6 receptor antibody, there was no reasonable expectation for successfully performing the claimed methods. Gijbels concluded that IL-6 targeted treatments were complex and unpredictable, and provided no reasonable expectation that a sensitized T-cell related disorder could be treated by targeting the IL-6 receptor. Vink showed that an antibody directed against IL-6 could not necessarily be replaced by an antibody directed against an IL-6 receptor. Samid never associated IL-6 activity with a sensitized T-cell mediated disease specified in the claims, and never suggested administering an antibody to treat such a disease. Samid bolsters the expectation of unpredictability in targeting IL-6 by reporting its extensive and pleiotropic effects. Accordingly, treating a sensitized T-cell mediated disease by targeting an IL-6 receptor was unpredictable, and therefore, there was no reasonable expectation for successfully performing the claimed methods.

Accordingly, the basis for this rejection may be withdrawn.

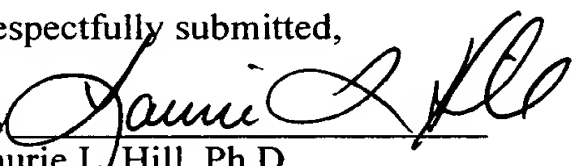
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 350292000800. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 29, 2005

Respectfully submitted,

By 

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